#19
1-10-01
RP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re **Chisari et al.**		
Serial No.:	08/854,825	
Filing Date:	May 12, 1997	
For:	**HEPATITIS C VIRUS-DERIVED PEPTIDES CAPABLE OF INDUCING CYTOTOXIC T LYMPHOCYTE RESPONSES**	**DECLARATION UNDER RULE 132 (to traverse a ground for rejection)**
Docket No.:	329368-101A	
Art Unit:	1648	
Examiner:	Parkin, J.S.	

Assistant Commissioner for Patents
Washington, DC 20231

I, Francis V. Chisari, M.D. an inventor of the above-referenced application ("the `875 application"), state as follows:

1. Information on my research credentials can be found in the attached *Curriculum vitae* (Exhibit A). My scientific peers have recognized my research on molecular virology and immunology by awarding me the Ernst Jung-Preis für Medizin in 1997 and the Rous-Whipple Award from the American Society for Investigative Pathology in 1998.

2. I am familiar with the Office Action in the `825 application dated February 2, 2000. In particular, I am familiar with the rejection that asserts that the specification does not reasonably enable a person skilled in the art to which it pertains to make or use an invention commensurate in scope with such claims as pending claim 22.

3. Pending claim 22 recites:

> 22. An isolated molecule comprising a polypeptide that induces an hepatitis C virus (HCV)-specific response in cytotoxic T lymphocytes having a sequence that

(a) ***has no more than a total of two single amino acid substitutions, deletions or insertions*** at the corresponding amino acid positions in a CTL epitope which is

(1) LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2),
(2) QLRRHIDLLV ($E1_{257-266}$; SEQ ID NO:3),
(3) KLVALGINAV ($NS3_{1406-1415}$; SEQ ID NO:28), or
(4) LLFNILGGWV ($NS4_{1807-1816}$; SEQ ID NO:35), or

(b) ***has no more than one single amino acid substitution, deletion or insertion*** at the corresponding amino acid positions as in a CTL epitope which is

(5) ADLMGYIPLV ($Core_{131-140}$; SEQ ID NO:1),
(6) DLMGYIPLV ($Core_{132-140}$; SEQ ID NO:54),
(7) LLCPAGHAV ($NS3_{1169-1177}$; SEQ ID NO:26),
(8) SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34), or
(9) ILDSFDPLV ($NS5_{2252-2260}$; SEQ ID NO:42),

wherein said molecule comprises at least eight amino acids and less than 50 amino acids, with the provisos that (i) when said selected CTL epitope is (8) SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34), then said molecule comprises from at least eight amino acids to less than 25 amino acids, (ii) when said selected CTL epitope is (1) LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2) then said molecule comprises at most ten amino acids, and (iii) when said selected CTL epitope is (6) DLMGYIPLV ($Core_{132-140}$; SEQ ID NO:54), then said molecule comprises at most nine amino acids.

(Emphasis added.)

4. This exemplary claim 22 allows for a very modest amount of variation from the core sequences identified therein.

5. The rejection applies even other particularly focused claims such as claim 65, which reads:

> 65. An isolated molecule comprising a polypeptide that induces an hepatitis C virus (HCV)-specific response in cytotoxic T lymphocytes having a sequence that has
>
> (a) no more than a total of two single amino acid substitutions, deletions or insertions at the corresponding amino acid positions in a CTL epitope which is
>
> LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2),
> QLRRHIDLLV ($E1_{257-266}$; SEQ ID NO:3),
> KLVALGINAV ($NS3_{1406-1415}$; SEQ ID NO:28), or
> LLFNILGGWV ($NS4_{1807-1816}$; SEQ ID NO:35), or

(b) has no more than one single amino acid substitution, deletion or insertion at the corresponding amino acid positions as in a CTL epitope which is

ADLMGYIPLV ($Core_{131-140}$; SEQ ID NO:1),
DLMGYIPLV ($Core_{132-140}$; SEQ ID NO:54),
LLCPAGHAV ($NS3_{1169-1177}$; SEQ ID NO:26),
SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34), or
ILDSFDPLV ($NS5_{2252-2260}$; SEQ ID NO:42),

wherein said polypeptide comprises at least eight amino acids and less than 50 amino acids, wherein said selected CTL epitope maintains an

`XaaLeuXaaXaaXaaXaaXaaXaaVal` or
`XaaLeuXaaXaaXaaXaaXaaXaaXaaVal` motif,

with the provisos that (a) when said selected CTL epitope is SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34), then said polypeptide comprises from at least eight amino acids to less than 25 amino acids, (b) when said selected CTL epitope is LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2) then said molecule comprises at most ten amino acids, and (c) when said selected CTL epitope is DLMGYIPLV ($Core_{132-140}$; SEQ ID NO:54), then said molecule comprises at most nine amino acids.

6. In my opinion, there was ample guidance in the art, as measured at the time of filing in March of 1994, and in my specification to allow the invention of the above-recited exemplary claims to be practiced without using more than an amount of experimentation that is usual in the art of molecular immunology.

7. For example, the Reece et al. article, which is of record in this application, and which is dated prior to the filing of this application, illustrates that the quantity of experimentation necessary to make and use the present invention was manageable when this application was filed in view of the technology then available. Reece et al., 151 J. IMMUNOL. 6175 (1993) (attached as Exhibit B). In Reece, in excess of one thousand (1,304) overlapping 12 residue peptide fragments were synthesized by the multipin method to map T-cell epitopes of tetanus toxin. Pools of 20 peptides each were used to simplify the mapping assays. (Such a pooling approach is endorsed in my specification for this application at page 16, lines 18-21.) Thus, it was practical to synthesize a large number of peptides, and the initial screen needed only to assay sixty to seventy pools. Pools that generated strong responses were deconvoluted by assaying the members of the pool.

8. The type of experimentation described by Reece could be readily applied to the build variants of the core peptides set forth in my claims, and identify the variants that meet my claims. The cytotoxicity assay described in my specification could be used to identify active pools, and subsequently identify the active peptides from the active (or particularly active) pools. Preferably, peripheral blood monocytes ("PBMCs") are used from a sampling of patients infected with hepatitis C virus ("HCV"), since, as my specification discusses, an antigen can be useful even if not active for all patients.

9. In Reece, the assay used was a PBMC proliferation assay to achieve the relatively high throughput required to assay a number of peptide pools. While I believe that other assays, including cytotoxicity, could in the relevant time frame have been used to achieve a useful amount of screening, Reece's screen would have been recognized as providing a useful initial screen.

10. The types of mapping experiments described by Reece were usual in the relevant time frame. See, for example, Sette et al., 328 NATURE 395 (1987) (attached as Exhibit C); Maryanski et al., 60 CELL 63 (1990) (attached as Exhibit D); and Takahashi et al., 170 J. EXP. MED. 2023 (1989) (attached as Exhibit E). The Sette (see Figure 1), Maryanski (see Table 1) and Takahahi (see Table II) articles are about exactly the kind of mapping experiments relevant to practicing the claimed invention using ordinary experimentation. As discussed in the specification of my patent application:

> In addition, the contributions made by the side chains of the residues can be probed via a systematic replacement of individual residues with a suitable amino acid, such as Gly or Ala. Systematic methods for determining which residues of a linear amino acid sequence are required for binding to a specific MHC protein, one of the characteristics of the peptides of the present invention, are known. See, for instance, Allen et al., Nature, 327, 713-717; Sette et al., Nature, 328, 395-399; Takahashi et al., J. Exp. Med., 170, 2023-2035 (1989); and Maryanski et al., Cell, 60, 63-72 (1990).

11. Further guidance to help avoid undue experimentation are the conclusions of Falk et al. on the binding preference of HLA-A2.1, based on extracted bound peptides:

> The second position contained a strong signal for Leu and an intermediate one for Met. Positions 3-5 had 6-8 residues each.

> Position 6 contained Val, Leu, Ile and Thr. Each of the following two positions had three signals. Position 9 had a strong Val and a weak Leu signal.

Falk et al., 351 NATURE 290 (1991) (attached as Exhibit F). More detailed guidance is found in the data of Table 4 of the Falk article.

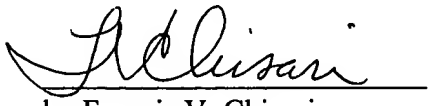
12. Moreover, the pooled peptide technique of Reece can be used to present relevant pools to peripheral blood monocytes, and extract peptides from MHC complexes, thereby identifying peptides that are actually presented by MHC molecules This information identifies stronger candidate peptides for use in cytotoxicity assays.

13. Still further guidance could be found by looking to the natural variations corresponding to the recited core sequences, of which there was not insubstantial knowledge in the relevant time frame. See, Houghton et al., 14 HEPATOLOGY 381 (1991) (attached as Exhibit G); and Ching et al., 89 PROC. NATL. ACAD. SCI. USA 3190 (1992) (attached as Exhibit H).

14. In conclusion, in the relevant time frame there were ample tools with which to practice the invention using ordinary experimentation. The literature of the era confirms that the experimentation described here was ordinary to the art of molecular immunology.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

July 25, 2000
Dated



by Francis V. Chisari

Curriculum Vitae

July, 2000

FRANCIS V. CHISARI, M.D.

Professor

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Date of Birth: April 5, 1942

Place of Birth: New York, New York

Citizenship: USA

Marital Status: Married, Linda Kornet, two children

Education: B.A., Magna cum laude, Fordham University, 1963

M.D., Cornell University Medical College, 1968

Scholastic Honors: Phi Beta Kappa, 1963; Alpha Omega Alpha 1967

Training:

Anatomic Pathology: Fellow, Cornell University Medical College, New York, 1966-1967.

Fellow, Mayo Clinic, Rochester, Minnesota 1969-1970.

Internal Medicine: Intern, The New York Hospital-Cornell University Medical Center, New York, New York 1968-1969.

Resident, Mary Hitchcock Memorial Hospital, Dartmouth Medical School, Hanover, New Hampshire 1972-1973.

Immunopathology: Staff Associate, Laboratory of Pathology, Division of Biological Standards, National Institutes of Health, Bethesda, Maryland 1970-72.

Research Fellow, Department of Experimental Pathology, Scripps Clinic and Research Foundation, La Jolla, California 1973-1975.

Molecular Biology: Fogarty Scholar, Unite de Recombinaison et Expression Genetique, Institut Pasteur, Paris, France 1983-1984.

Board Certification: Internal Medicine, 1973; Anatomic Pathology, 1975.

National Service: United States Public Health Service, National Institutes of Health, Bethesda, Maryland 1970-1972.

Employment:

1975-1981	Assistant Professor, Departments of Molecular Immunology and Clinical Research, Scripps Clinic and Research Foundation, La Jolla, California
1976-1981	Assistant Adjunct Professor, Department of Pathology, University of California, San Diego School of Medicine, La Jolla, California
1976-1983	Head, Division of Diagnostic Immunopathology, Department of Pathology, Green Hospital of Scripps Clinic, Scripps Clinic and Research Foundation, La Jolla, California
1981 - 1988	Associate Professor, Department of Basic and Clinical Research, Research Institute of Scripps Clinic, La Jolla, California
1982-1987	Associate Adjunct Professor, Department of Pathology, University of California, San Diego, School of Medicine, La Jolla, California
1984-1989	Associate Director, General Clinical Research Center, Research Institute of Scripps Clinic, La Jolla, California
1987-1998	Adjunct Professor, Department of Pathology, University of California, San Diego, School of Medicine, La Jolla, California
1988-Present	Professor and Head, Division of Experimental Pathology, Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California
1989-Present	Director, General Clinical Research Center, The Scripps Research Institute, La Jolla, California

Review Committees and Advisory Boards:

-Pathology B Study Section and Reviewers' Reserve, National Institutes of Health, 1988-1992

-Zoological Society of San Diego: Research, Animal Health, Conservation Committee, 1986-90

-Scientific Advisory Board, DNX Corporation, Princeton, New Jersey, 1989-1993

-Scientific Review Board, German Cancer Research Center, Heidelberg, Germany, 1990-91

-Hepatitis Panel, US-Japan Cooperative Medical Science Program, 1992-1998

-Hepadnaviridae Study Group, International Committee and Taxonomy of Viruses, 1994-present
-Scientific Advisory Board, Liver Research Ctr., Albert Einstein Coll. of Medicine, 1995-2000
-Nominating Committee, American Society for Investigative Pathology, 1999-present
-Distinguished Advisory Committee, UCSD Cancer Center, 2000-present

Editorial Positions:

American Journal of Pathology; American Journal of Physiology; Diagnostic Molecular Pathology; Gastrointestinal and Liver Physiology; Journal of Clinical Investigation; Journal of Experimental Pathology; Hepatology; inScight Daily Science News Service; Microbial Pathogenesis; Transgene; Transgenic Research; Viral Immunology; Virology.

Professional Societies:

Association of American Physicians, American Society for Virology, American Association of Immunologists, American Society for Investigative Pathology, American Association for Cancer Research, American Association for the Advancement of Science, American Federation for Clinical Research, Western Association of Physicians, American College of Physicians, Molecular Medicine Society.

Honors and Awards:

Research Career Development Award, NIH, 1976-1981.
Elected Member, Association of University Pathologists, 1978
Fogarty Senior International Fellowship, NIH, 1983-1984.
National Research Service Senior Fellowship, NIH, 1983-1984.
Foreign Scholar, Fondation pour la Recherche Medicale, Paris, France, 1984.
Honorary Member, Society of Medicine and Natural Sciences, Univ. of Parma, Italy, 1985.
MERIT Award, NIH, 1990-2000.
Elected Member, Association of American Physicians, 1992.
Sheila Sherlock Award for Excellence in Liver Research, University of Toronto, 1992.
Maud L. Menten Award in Experimental Pathology, University of Pittsburgh, 1996.
Elected Fellow, American Association for the Advancement of Science, 1996.
Ernst Jung Prize in Medicine, Jung-Stiftung für Wissenschaft und Forschung, Hamburg 1997.
First Distinguished Scientific Achievement Award, American Liver Foundation, 1997.
Rous-Whipple Award, American Society for Investigative Pathology, 1999.
Distinguished Achievement Award, American Association for the Study of Liver Diseases, 1999.
Elected Member, The Henry Kunkel Society, 1999.

ABSTRACTS

Named Lectureships:

Peter Ciano Memorial Lecture, Harvard Medical School, 1992.

Henry Moon Memorial Lecture, University of California San Francisco, April 1992.

Karl F. Meyer Lectureship in Microbiology, University of California San Francisco, 1997.

Shipley Symposium Lectureship in Microbial Pathogenesis, Harvard Medical School, 1997.

Bertram-Marx Lectureship in Microbiology, Univ. of Alabama, Birmingham, 1998.

Distinguished Lecturer in Medical Sciences, Mayo Clinic, 1999.

Saul Krugman Memorial Lectureship, Honors Lecture Series, New York University, 1999.

U.S. Patents

U.S. Patent 4,599,230; 4,599,231 (7/8/86)
Synthetic hepatitis B virus vaccine including both T cell and B cell determinants.

U.S. Patent 4,683,136 (7/28/87)
Proteinaceous antigens with conformation dependent determinants.

U.S. Patent 5,709,995 (1/20/98)
Hepatitis C virus-derived peptides capable of inducing cytotoxic T lymphocyte responses.

U.S. Patents 5,780,036 (7/14/98); 5,788,969 (8/4/98); 5,840,303 (11/24/98); 5,932,224 (8/3/99)
Peptides for inducing cytotoxic T lymphocyte responses to hepatitis B virus.

UCLA Symposium: Animal Models of Human Diseases; Transgenic Modeling of HBV Pathogenesis, Keystone, CO, March 1990

American Association for the Study of Liver Diseases Conference on Immunobiology and the Liver; Immunologically Mediated Liver Cell Injury in HBV Infection, Washington, DC, April, 1990

Chairman, Symposium on Transgenic Models of Cell Injury, FASEB Conference, Washington, DC, April 1990

International Symposium on Viral Hepatitis; Immunopathogenesis of Viral Hepatitis, Houston, TX, April 1990

International Papillomavirus Workshop; Expression of DNA Tumor Viruses in Transgenic Mice, Heidelberg, Germany, May 1990

15th International Cancer Congress of the International Union Against Cancer, Session Chairman, Symposium on Hepadnavirus and Primary Liver Cancer, Hamburg, August 1990

UCSD Symposium on Molecular Biology of Hepatitis B Viruses, Session Chairman, Immunobiology and Pathogenesis, San Diego, CA, August, 1990

13th International Congress of Virology, Berlin, Germany, August 1990

Cold Spring Harbor Symposium, Origins of Human Cancer, New York, NY, September 1990

Workshop on Hepatocellular Carcinoma, National Institutes of Health, Bethesda, MD, September 1990

ABSTRACTS

Concepts in Molecular Biology, course sponsored by the National Cancer Institute and the American Association of Pathologists, Bethesda, MD, November 1990

Symposium on Cellular Growth and Malignancy, Coordinating Council for Cancer Research, Massachusetts General Hospital Cancer Center, Boston, MA, April 1991

US-Japan Cooperative Science Program on Viral Hepatitis, New York, NY, May 1991
University of Rome Symposium on Chronic Viral Hepatitis, Rome, Italy, May 1991

International Symposium on Gene Expression during Liver Differentiation and Disease, Sorrento, Italy, June, 1991

FASEB Summer Research Conference on Molecular Mechanisms of Carcinogenesis, Saxton's River, Vermont, July, 1991

Institut Pasteur Symposium on Molecular Biology of Hepatitis B Viruses, Paris, France, October 1991

Concepts in Molecular Biology, course sponsored by the National Cancer Institute and the American Association of Pathologists, Bethesda, MD, November 1991

Co-organizer, AFIP-UAREP Symposium on Transgenic Animal Models, Washington, DC, November 1991.

First AACR/EACR Joint Conference on Concepts and Molecular Mechanisms of Multistage Carcinogenesis, Santa Margherita, Italy, November 1991

Third International Symposium on Viral Hepatitis and Hepatocellular Carcinoma, Taipei, Taiwan, ROC, December 1991

US-Japan Cooperative Science Program on the Molecular Genetics of Hepatocellular Carcinoma, Honolulu, Hawaii, February 1992

Keystone Symposium on Cell Biology of Virus Entry, Replication and Pathogenesis, Taos, NM, February 1992

UCI/ICN Symposium on Viral Latency and Persistence, Newport Beach, CA, March 1992

The 1992 International Symposium on Pathobiology of Viral Hepatitis and Liver Diseases, Tokyo, Japan, April 1992

US-Japan Cooperative Science Program on Viral Hepatitis, Tokyo, Japan, April, 1992

Henry Moon Memorial Lecture, Molecular Pathogenesis of Hepatocellular Carcinoma, University of California, San Francisco, April 1992

ABSTRACTS

Sheila Sherlock Liver Research Award Lecture, University of Toronto, Canada, May 1992

Immunology Seminar Series, Washington University School of Medicine, St. Louis, MO, May 1992

Monsanto Company, St. Louis, MO, May 1992

FASEB Summer Conference on Liver Regeneration and Hepatocarcinogenesis, Session Chairman., Copper Mountain, CO, July 1992

Genentech, Inc., So. San Francisco, CA, August, 1992

Molecular Biology of Hepatitis Viruses, Meeting Organizer, San Diego, CA September 1992

Falk Symposium on Immunology and the Liver, Basel, Switzerland, October 1992

"Hepatitis B virus: Molecular biology and markers". UCSD Basic Science and Pathology Seminar, Hepatitis B Virus: Molecular Biology and Markers, San Diego, CA, January 6, 1993

"Viral expression and hepatocarcinogenesis in hepatitis B virus transgenic mice". Triangle Virology Club at Duke University, January 27, 1993.

"Cytotoxic T cell response to hepatitis B virus in man and the transgenic mouse". University of North Carolina School of Medicine, Virology Department Lecture, Chapel Hill, N.C., January 28, 1993

"Liver Fibrosis and hepatocellular carcinoma". UCSD Basic Science and Pathology Seminar, Liver Fibrosis and Hepatocellular Carcinoma, San Diego, CA, February 3, 1993

"Cytotoxic T cell mediated fulminant hepatitis in hepatitis B virus transgenic mice", Western Association of Physicians Annual Meeting, Carmel, CA February 17-18, 1993

"The HLA class I restricted cytotoxic T lymphocyte response to the hepatitis B virus". Keystone Symposium, Molecular Immunology of Virus Infections, Taos, N.M., March 21, 1993.

"HBV-transgenic mouse systems". Cold Spring Harbor Laboratories Biannual Liver Conference, Regulation of Liver Gene Expression in Health and Disease, Cold Spring Harbor, N.Y., May 5-9, 1993.

"Pathogenesis for viral and autoimmune hepatitis". 8th Triennial Congress, International Symposium on Viral Hepatitis and Liver Disease, Tokyo, Japan, May 10-14, 1993

"The transgenic mouse model for the study of HBV pathogenesis". Biology, Immunopathology and Clinic of Hepatitis Viruses, Parma Italy, June 3-5, 1993

ABSTRACTS

"Class I restricted immunopathogenesis is a multistep process in HBsAg transgenic mice". 1993 Meeting on the Molecular Biology of Hepatitis B Viruses, Georgetown University, Rockville, MD August 1-5, 1993

"Mechanisms of hepatocarcinogenesis in hepatitis B virus infection". Viruses in Cancer Symposium, Harvard School of Medicine, Boston, MA, Oct. 15, 1993

"The HLA class I restricted cytotoxic T lymphocyte response to the hepatitis B virus in man and transgenic mice". 1993 Hepatitis Symposium, Abbott Laboratories, Abbott Park, IL Nov. 1-3, 1993

"The cytotoxic T cell response in the hepatitis B virus in man and transgenic mice". Biogen Symposium-Interferon Response and Immunity to Hepatitis Virus, Cambridge, MA, Nov. 12, 1993.

"The class I restricted CTL response to predetermined epitopes in hepatitis B and C viruses". T Cell Mediated Immunity to Hepatitis C Virus Minisymposium, Chiron Corporation, Emeryville, CA Dec. 2-3, 1993

"Immunobiology and Pathogenesis of Hepatitis B in Humans and Transgenic Mice". University of California at Los Angeles, Department of Microbiology and Immunology, Los Angeles, CA January 10, 1994.

"Lymphocyte effector function." The 33rd Midwinter Conference of Immunologists, Asilomar, CA, January 22-25, 1994.

"Immunobiology and pathogenesis of hepatitis B virus infection". The VIth International Symposium on Viral Hepatitis in Madrid, Spain, Feb. 3-5, 1994.

"A transgenic mouse model of viral hepatitis". American Society for Investigative Pathology Workshop on Hepatitis Injury Responses and Carcinogenesis. Anaheim, CA, Apr. 24, 1994.

"Hepatitis B virus immunobiology and pathogenesis". Virology Course, Rockefeller University, New York, N.Y., May 5, 1994.

"Hepatitis B virus: Cytotoxic T cell responses in man and transgenic mice". Immune Response Corp., Carlsbad, CA, Sep. 14, 1994.

"Can cytotoxic T lymphocytes destroy the hepatitis B virus without killing the infected cell?" Molecular Biology of Hepatitis B Virus Meeting, Paris, France, Oct. 3-6, 1994.

"Can cytotoxic T lymphocytes inactivate the hepatitis B virus without killing the cell?" IRIS Symposium "Molecular Mechanisms of Microbial Pathogenesis", Siena, Italy, Oct. 23-26, 1994.

"Viral mechanisms of liver injury". Fourth Annual Irwin M. Arias M.D. Symposium (American Liver Foundation), "Bridging Basic Science and Liver Disease," Boston, MA, Nov. 9, 1994.

ABSTRACTS

"HBV immunobiology and pathogenesis in transgenic mice" Innovir Laboratories, New York, N.Y., Nov. 10, 1994.

"Molecular Aspects of Viral induced inflammatory disease". Keystone Symposium-Molecular Aspects of Viral Immunity, Jan. 16-20, 1995.

"Intracellular inactivation of the hepatitis B virus by the immune response". U.S.-Japan Cooperative Hepatitis Panel Meeting, Tokyo, Japan, Jan. 23-24, 1995.

"Intracellular inactivation of hepatitis B virus replication by the immune response". Immunology Seminar Series, Massachusetts General Hospital, Boston, MA, May 11, 1995.

"The curative immune response to hepatitis B virus". American Association for the Study of Liver Diseases, Digestive Diseases Week State-of-the-Art Lecture, San Diego, CA, May 16, 1995.

"Intracellular inactivation of the hepatitis B virus by immune response". 1995 Gordon Research Conference, Viruses and Cells (Pathogenesis Session Chairman), Tilton, NH June 12, 1995

"Immunopathogenesis of hepatitis B virus infection". 1995 Annual meeting of the Italian Association for the Study of the Liver, Rome, Italy, June 15-16, 1995.

"Antiviral effects of HBV DNA-based immunization in transgenic mice that replicate the hepatitis B virus". The Molecular Biology of Hepatitis B Viruses Meeting, San Diego, CA, July 23-27, 1995.

"Intracellular inactivation of the hepatitis B virus by the immune response". 9th International Congress of Immunology, San Francisco, CA, July 25, 1995.

"The cytotoxic T lymphocyte response to the hepatitis C virus". Third International Symposium on Hepatitis C Virus, and Fifth International Symposium on Hepatitis D Virus and Liver Disease (Immunology and Pathogenesis Session Chairman), Queensland, Australia, August 28-September 3, 1995.

"Immune activation of intracellular pathways for the clearance of HBV". Pasteur 100th Anniversary Meeting on Vaccines. Institut Pasteur, Paris, France, September 24-28, 1995.

"Intracellular inactivation of the hepatitis B virus by the immune response". Hepatitis B virus Therapeutics Workshop, Hepatitis B Foundation, Jefferson Medical College, Princeton, NJ, September 28, 1995.

"Intracellular inactivation of the hepatitis B virus by the immune response". Bristol-Myers Squibb Symposium on the Molecular Pathogenesis of Viruses, New York, N.Y., December 7-8, 1995.

ABSTRACTS

"Cytopathic and noncytopathic pathways for immune mediated clearance of the hepatitis B virus by cytotoxic T lymphocytes and inflammatory cytokines". U.S.-Japan Hepatitis Panel Meeting, Kona, Hawaii, Jan. 16-17, 1996.

"Hepatitis B virus specific cytotoxic T lymphocyte responses following recovery from acute and chronic HBV infection", U.S.-Japan Hepatitis Panel Meeting, Kona, Hawaii, Jan. 16-17, 1996.

"Pathogenetic and curative aspects of the immune response to hepatitis B virus" University of Southern California Center for Liver Diseases, Los Angeles, CA, Feb. 8, 1996.

"To kill or to cure: Options in host defense against viral infections". Fifteenth Maud L. Menten Lecture, University of Pittsburgh School of Medicine, Department of Pathology, Pittsburgh, PA, Feb. 21, 1996.

"To kill or to cure: Options in host defense against viral infections". Concepts in Biology and Medicine: The Scripps Research Institute Faculty Lecture Series 1996, the Scripps Research Institute, La Jolla, CA, April 9, 1996.

"Intracellular inactivation of the hepatitis B virus by the immune response". Bristol-Myers Squibb Seminar Series, New York, N.Y., Apr. 19, 1996.

"Pathogenesis of Viral Hepatitis". IX Triennial International Symposium on Viral Hepatitis and Liver Disease, Rome, Italy, Apr. 21-25, 1996.

"CTL in HBV infection: Noncytolytic clearance mechanisms." Meeting of Investigators in HIV-Specific CTL, Annecy, France, May 21, 1996.

"To Kill or to Cure: Options in Host Defense against Viral Infections." Mini-Symposium: Potential Impact of an Immunomodulator for Treatment Of Viral Diseases, Pfizer, Inc., Groton, CT, Sept. 4, 1996.

"To Kill or to Cure: Options in Host Defense against Viral Infections." Rockefeller University Friday Lectures, Rockefeller University, New York, NY, Sept. 6, 1996.

"Intracellular Inactivation Of The Hepatitis B Virus By The Immune Response". McArdle Colloquium Series, University of Wisconsin-Madison, Madison, WI, Sept. 17, 1996.

"MHC Class II Restricted T Cells Can Cause Hepatitis And Suppress Viral Replication In HBV Transgenic Mice." Cold Spring Harbor Symposium on Molecular Biology of Hepatitis B Viruses, Cold Spring Harbor, NY, Sept., 1996.

DNA Vaccines and Cytokines." Princeton Workshop: Therapeutic Strategies for HBV Disease,Hepatitis B Foundation, Princeton, NJ, Sept. 23, 1996.

"Intracellular Inactivation Of The Hepatitis B Virus By The Immune Response." Stanford University Department of Microbiology and Immunology Seminar Series, Stanford University, Stanford, CA, Oct. 11, 1996.

ABSTRACTS

"Hepatitis B Virus Immunology And Pathogenesis." Annual Meeting of the Argentine Society for Immunology, Buenos Aires, Argentina, Oct., 1996.

"Immunological Mechanisms Of Viral Clearance In HBV Transgenic Mice." American Association for the Study of Liver Diseases Research Workshop, Chicago, IL, Nov. 10, 1996.

"Intracellular Inactivation Of The Hepatitis B Virus By The Immune Response." U.S.-Japan Hepatitis Panel Meeting, Nagasaki, Japan, Nov. 16, 1996.

"To Kill or to Cure: Options in Host Defense against Viral Infections." K.F. Meyer Memorial Lecture, University of California-San Francisco, San Francisco, CA, Feb. 26, 1997.

"Control of hepatitis B virus replication by the immune response." Gene Expression in Cellular and Viral Systems, University of Heidelberg, Germany, February 27, 1997.

"Hepatitis B virus inactivation by CTL and inflammatory cytokines." 1st Kanazawa International Symposium on Cancer, Kanazawa, Japan, March 11, 1997.

"Regulation of hepatitis B virus gene expression and replication by the immune response." Spring Seminar, Istituto Ricerche Di Biologia Molecolare, Rome, Italy, April 1-2, 1997.

"Pathogenesis of persistent HBV infection." 32nd Annual Meeting, European Association for the Study of Liver Disease, London, UK, April 9-12, 1997.

"Hepatitis B virus inactivation by cytotoxic T lymphocytes and inflammatory cytokines." Regulation of Liver Gene Expression in Health and Disease, Cold Spring Harbor, NY, April 30-May 4, 1997.

"Hepatitis B virus inactivation by cytotoxic T lymphocytes." 16th Annual Meeting, American Society for Virology, Bozeman, MT, July 19-23, 1997.

"Immunological basis of hepatocellular carcinoma in hepatitis B virus transgenic mice." Molecular Biology of Hepatitis B Viruses, Institut Pasteur, Paris, France, September 21-25, 1997.

"Mouse Models of Viral Hepatitis: Insights into persistence and pathogenesis." 2nd International Meeting on Therapy in Liver Diseases, Barcelona, Spain, September 17-19, 1997.

"Intracellular Viral Inactivation During the Immune Response." Shipley Symposium Lectureship in Microbial Pathogenesis, Harvard Medical School, Cambridge, MA, November 21, 1997.

"Intracellular Viral Inactivation During the Immune Response." Virology Seminar Series, University of California - Irvine, Irvine, CA, December 5, 1997.

"Antiviral Immunity: The Hepatitis B Virus Paradigm." USC Spring Seminar Series, University of Southern California, Los Angeles, CA, April 2, 1998.

ABSTRACTS

"Immune Control of Hepatitis B Virus Infection." Stanford Spring Seminar Series, Stanford University School of Medicine, Palo Alto, CA, April 14, 1998.

"Immunological Control of Hepatitis B Virus Infection." National Institutes of Health, Bethesda, MD, April 30, 1998.

"Intracellular Inactivation of the Hepatitis B Virus by the Immune Response." Infectious Disease and Society, State University of New York at Stony Brook, Stony Brook, New York, April 23-24, 1998.

"New Concepts in Viral Pathogenesis: The Hepatitis B Virus Paradigm." University College Dublin, Dublin, Ireland, May 26, 1998.

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